

## CARDIOMYOPATHY

Neglected  
cardiomyopathies in Africa*Ana Olga H. Mocumbi*

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**INTRODUCTION**

Cardiomyopathies are forms of disease in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valve disease and congenital heart disease sufficient to explain the observed myocardial abnormality.<sup>(1)</sup>

The diseases of the heart muscle constitute the greatest challenge of all the cardiovascular diseases in Africa<sup>(2)</sup> where, in addition to the cardiomyopathies usually seen in the developed world, there is a high prevalence of specific forms of myocardial disease which cause considerable morbid-mortality and affect large numbers of people, but have not been the subject of enough attention from the medical and research communities. They are part of the forgotten or neglected cardiovascular diseases.

The most striking example of neglected cardiomyopathy is Endomyocardial Fibrosis (EMF).<sup>(3)</sup> Despite being the most common form of restrictive cardiomyopathy worldwide, affecting an estimated 12 million people,<sup>(4)</sup> EMF has received little attention from the scientific community as shown by the declining number of publications on the subject in the last decades.<sup>(5)</sup>

**ABSTRACT**

**Cardiomyopathies are forms of disease in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valve disease and congenital heart disease sufficient to explain the observed myocardial abnormality. They constitute the greatest challenge of all the cardiovascular diseases in Africa, due to the difficulties in diagnosing and managing them, related to the lack of access to specialised investigations or effective interventions in most endemic areas.**

**In this continent, in addition to the “usual” forms of cardiomyopathy, there is an increased incidence of specific forms of muscle heart disease like Endomyocardial Fibrosis and Peripartum Cardiomyopathy which, despite affecting thousands of people, have been largely neglected. Their etiology remains unknown, the mechanisms involved are not fully understood, and although some improvement in management has been witnessed in recent years much still need to be done to improve the outcome.**

**The current knowledge on epidemiology, determinants, pathophysiology, diagnosis and management of Endomyocardial Fibrosis and Peripartum Cardiomyopathy is reviewed in this article, which also presents the ongoing efforts for better understanding of their pathogenesis and the recent improvements in their management. SAHeart 2009; 6:30-41**

**Size of the problem**

Cardiomyopathies constitute a huge burden to both communities and health systems in Africa. Together with rheumatic heart disease, tuberculous pericarditis, systemic hypertension and its complications, cardiomyopathies are the major causes of heart disease in black African populations, causing great morbidity and mortality in young and economically active people<sup>(6,7)</sup> and being responsible for more than 20% of all admissions for cardiovascular diseases in both children and adults.<sup>(8)</sup>

EMF, the most common cardiomyopathy in African children and adolescents, shows great geographic variation with areas of higher incidence being the tropical regions of East, Central and West of the continent,<sup>(9)</sup> where it accounts for up to 20% of cases of heart failure.<sup>(5,7,10)</sup> This regional variation in prevalence

occurs for reasons that are unclear<sup>(5)</sup> and within country regional variation has also been reported in Mozambique,<sup>(11)</sup> Uganda<sup>(12)</sup> and Nigeria.<sup>(13)</sup>

Several studies in African countries revealed an incidence of Peripartum Cardiomyopathy (PPCM) varying from 1:500 to 1:1000 deliveries.<sup>(14,15,16)</sup> This cardiomyopathy is known to have high incidence and prevalence in the black race,<sup>(17,18,19)</sup> and studies in the USA have shown that African-American women had 2.9-fold more cases of PPCM when compared with whites and 7-fold more cases than Hispanic women.<sup>(20)</sup>

A new challenge for African countries is the HIV-related cardiomyopathy, which constitutes the most important cardiovascular manifestation of HIV infection with a prevalence varying from 10% to 30% in echocardiography or autopsy studies.<sup>(21,22,23)</sup> Its incidence increases with the progression of AIDS<sup>(22,23,24,25)</sup> and is likely to become even more prevalent as HIV-infected patients live longer: Rapid progression to death in less than 3 months has been reported in patients without antiretroviral therapy<sup>(26)</sup> either due to HIV-myocarditis or to opportunistic infections, autoimmune response to viral infection, and nutritional deficiencies.<sup>(25,26,27,28)</sup> Dilated cardiomyopathy is now the leading cause of heart disease in acutely ill hospitalised patients with HIV in Africa,<sup>(29,30)</sup> particularly in those not receiving highly active antiretroviral therapy.<sup>(31)</sup> The advent of highly active antiretroviral therapy has had an impressive impact on mortality and disease progression in developed countries, but these effects are not yet seen in Africa due to lack of universal access to therapy. Similarly to other parts of the globe, some antiretroviral drugs have several side effects that can lead to cardiac dysfunction.<sup>(32)</sup>

Although important due to the high number of people at risk in Africa, we will not discuss HIV-related cardiomyopathy in detail. Instead we will concentrate in reviewing the current knowledge on Endomyocardial Fibrosis and Peripartum Cardiomyopathy.

## ENDOMYOCARDIAL FIBROSIS

### Definition

Endomyocardial Fibrosis (EMF) is an extremely debilitating disease, classified as a restrictive cardiomyopathy that is characterised by endocardial fibrous thickening, affecting predominantly the

ventricular wall and the atrioventricular valves, which results in ventricular cavity reduction with abnormal diastolic filling, and severe tricuspid or mitral regurgitation.

### Etiology and determinants

The etiology of EMF remains unknown although several factors have been implicated in its origin. Ethnicity, poverty, malnutrition, dietary factors, infections (viral and parasitic), autoimmunity, allergy (eosinophilia), toxic agents (cerium, cassava, serotonin, plant toxins and vitamin D) and heredity have all been implicated.<sup>(5)</sup>

The major determinants of EMF seem to be age, gender, ethnic group, social deprivation and eosinophilia.<sup>(12,33,34,35)</sup> This condition affects predominantly children with more than half the cases being diagnosed during the first decade of life.<sup>(36)</sup> However, it can occur in infants<sup>(37)</sup> and a second peak incidence occurs in women of childbearing age.<sup>(4)</sup>

Childhood EMF affects both sexes.<sup>(38)</sup> Female preponderance has been found in young adults from Uganda<sup>(39)</sup> while in Mozambique males are more affected.<sup>(33)</sup>

Regarding ethnics, studies from Uganda reported preponderance of the condition in patients from Rwanda and Burundi that immigrate to the Southwest.<sup>(12,40)</sup> In Mozambique, an analysis of referrals to a tertiary unit showed a striking high attack rate in an ethnic group from a rural coastal area in the south of the country,<sup>(11)</sup> for reasons that could not be determined.

Familial cases of EMF have been described in both clinical<sup>(41,42)</sup> and epidemiological studies.<sup>(33)</sup> The most important conditioning factors seem to be environmental.<sup>(9,43)</sup> However, preliminary results of studies performed in Mozambican patients with EMF showed evidence of immunogenetic heterogeneity (Mocumbi, unpublished data).

The role of infectious agents has been mainly supported by findings of sporadic cases of EMF in foreign people from temperate areas after short stays in endemic regions,<sup>(44,45)</sup> but it also appears plausible in view of climatic restrictions of the disease. Plasmodium species,<sup>(46)</sup> Schistosoma,<sup>(47)</sup> Microfilaria,<sup>(48)</sup> Helminths,<sup>(35)</sup> Coxsackie B virus,<sup>(49)</sup> Arboviruses and Toxoplasma gondii<sup>(49)</sup> have all been considered as possible causes or triggers for disease.

Regarding the role of autoimmunity, studies in African populations showed evidence of higher prevalence of antiheart antibodies in EMF patients when compared to those with rheumatic heart disease, dilated cardiomyopathy and healthy controls.<sup>(46)</sup> However, it is not clear if these autoantibodies are the cause or the result of EMF, and pathological studies failed to show large numbers of immunologically competent cells at the endomyocardial junction, where EMF lesions are more prominent.<sup>(50)</sup>

New evidence for autoimmunity was found in a large subset of EMF patients from Mozambique which serum was tested for the presence of anti-myocardial proteins. Strong reactivity against myocardial proteins was found (Mocumbi unpublished data) corroborating findings from India.<sup>(51)</sup> Although weaker, there was also increase in IgM reactivity when EMF patients were compared to healthy controls of the same population.

None of these hypotheses is by itself sufficient to explain the non-random geographical occurrence of EMF worldwide, nor can any of them explain the pathological findings characteristic of this condition.

## Pathophysiology

Endomyocardial fibrosis appears to start as a febrile episode triggered by an unknown factor followed by ventricular thrombosis which can be associated with facial swelling, body itching, hyper-eosinophilia and thromboembolism.<sup>(52,35)</sup> It is thought that mural and valvar thrombosis evolves to organisation of the thrombus and endocardial fibrosis, affecting mainly the ventricular apices and the recess behind the posterior leaflet of the mitral valve.<sup>(39)</sup> Mural endocardial fibrosis reduces ventricular cavity size and impedes adequate filling leading to restrictive physiology, while fibrosis of the endocardium affecting the papillary muscles, chordae and/or leaflets causes valve distortion, resulting in severe atrio-ventricular regurgitation. These two abnormalities are responsible for the typical aspect of small ventricles with severely dilated atria found in this entity.

The sustained low cardiac output results in finger and toe clubbing, growth retardation, testicular atrophy, failure to develop male secondary sexual characters and cachexia.<sup>(53,54,55,56)</sup> In right ventricular EMF, the most common form of presentation either in isolation or as part of biventricular disease, chronic systemic venous hypertension leads to exophthalmos, elevated jugular

pressure, gross hepatomegaly and congestive splenomegaly.<sup>(56)</sup> However, some distinctive features of EMF cannot be explained solely by low cardiac output and retrograde congestion. For instance, there is still some controversy regarding the pathophysiology of the central cyanosis and the voluminous ascites that can lead to ventral or inguinal hernia in the absence of pedal oedema.<sup>(57)</sup>

## Diagnosis

The clinical picture of EMF depends on the ventricle affected, the duration of disease and the presence of active disease. By the time of clinical presentation patients with EMF are usually at an advanced stage<sup>(36)</sup> and most give poor clinical history. Interestingly, patients can be mildly symptomatic while having severe structural abnormalities detected on echocardiography.<sup>(58,59)</sup>

Patients with right-sided EMF often present with exophthalmos, jaundice, peripheral cyanosis, finger clubbing, atrial fibrillation, ascitis without pedal oedema, third sound and absence of cardiac murmurs due to free tricuspid regurgitation.<sup>(36)</sup> In left-sided EMF there is usually a systolic murmur that is typically soft, short and confined to early systole, associated with a delayed opening snap, and a loud pulmonary component of the second sound, indicating increased pulmonary pressures.<sup>(60)</sup>

The biological profile of EMF patients is unspecific. Hyper-eosinophilia is a common finding<sup>(61)</sup> without any evidence of infection or parasitism.<sup>(62)</sup> The effusions, particularly the ascitic fluid, are typically exudates having more leukocytes (predominantly lymphocytes) and higher protein content than expected in right heart failure.<sup>(63)</sup>

The electrocardiogram shows no constant pattern. There are usually low voltage QRS complexes, non-specific ST-T wave changes, conduction disturbances and atrial arrhythmias in advanced disease.<sup>(61)</sup> A tall and broad right atrial wave, "qr" pattern in the leads V3R or VI, and delayed right ventricular conduction are characteristic of right EMF.<sup>(56,57)</sup>

The chest x-ray in right ventricular EMF shows severe right atrial enlargement, a bulge over the left heart border due to dilatation of the infundibulum, and hypoperfused lungs, while in left-sided EMF there is prominent main pulmonary artery, exaggeration of the blood vessels in the lung fields and left atrial enlargement.

Echocardiography is the most valuable tool for diagnosis and usually reveals dense endocardial echos along different parts of the mural and valvar endocardium, valve dysfunction and a restrictive filling pattern. Characteristically there is obliteration of the trabecular portion of the right ventricle and, in advanced cases, shrinkage of the cavity with an apical notch, free tricuspid regurgitation, signs of spontaneous contrast, right atrial thrombi and pericardial effusion (Figure 1). Left disease usually shows patchy enhancement of the endocardial echo, thickening of the endocardium of the LV apex that can be obliterated, plastered-down posterior mitral leaflet causing eccentric mitral regurgitation, a rapid early filling followed by restriction, and left atrial enlargement (Figure 2). The main criteria used for diagnosis of endomyocardial fibrosis are presented in Table 1.

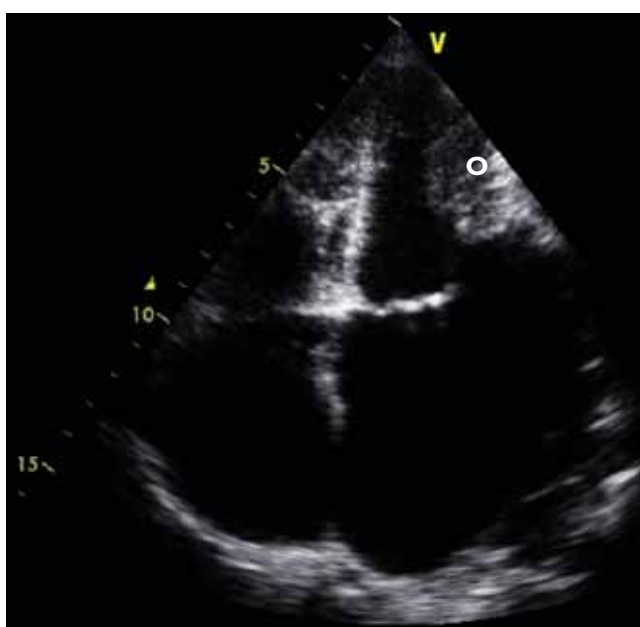
Computed tomography is seldom used in clinical practice since it adds little to the echocardiography. The presence of a linear calcification distal to the pericardium, along the inner border of the myocardium suggests EMF at conventional and spiral computed tomography.<sup>(64)</sup> Magnetic Resonance Imaging (MRI) confirms the

existence of thrombus or calcifications, allows an exact delineation of hypoperfused areas that correspond to fibrosis<sup>(65)</sup> and provides functional information,<sup>(65,66)</sup> but is not readily available in most endemic areas.<sup>(67)</sup>

Cardiac catheterisation is seldom used due to the imbalance between the information obtained and the risk of the procedure. It is not adequate for diagnosis of localised or mild forms of disease where tissue can be obtained from unaffected sites, and may be technically challenging in areas of dense endocardial fibrous thickening in advanced disease. The procedure is associated with (a) bleeding from venous puncture sites due to high venous pressure; (b) difficulty in entering the right ventricle and pulmonary artery due to markedly dilated right atrium, tricuspid regurgitation, small right ventricular cavity, and distorted and displaced right ventricular outflow tract; (c) high risk of pulmonary thrombo-embolism from right atrial thrombi; (d) and considerable risk of acute hemodynamic deterioration due to stimulation of atrial tachyarrhythmia. However, it can be useful in differentiating mild forms from early constrictive pericarditis.



**FIGURE 1:** Reduction of the ventricular cavity and the characteristic image of apical notch, associated with non-coaptation of the tricuspid leaflets, are frequent findings of REMF. There is marked spontaneous contrast and right atrial thrombi (**T**), as well as pericardial effusion. In severe cases the left cavities are compressed by the right cavities.



**FIGURE 2:** Thickening of the endocardium of the anterior mitral leaflet, the interventricular septum, subvalvar apparatus and apex of the LV. There is obliteration (**O**) of the posterior recess of the mitral valve with absence of the posterior mitral leaflet. There is reduction of the left ventricular volume and dilatation of the left atrium. Left cavities are compressed by the right cavities.

**TABLE 1:** Criteria used for diagnosis of established endomyocardial fibrosis

Right ventricular EMF	Left ventricular EMF
Thickened RV endocardium usually in septal and apical portions with adherent tricuspid valve apparatus	Thickened LV endocardium usually in the apex and posterior wall with plastered posterior mitral leaflet
Obliteration of trabecular portion of the RV	Obliteration of LV apex/posterior recess
TV dysfunction (mainly regurgitation)	MV dysfunction (mainly regurgitation)
Endocardial calcification on the right ventricle	Endocardial calcification on the left ventricle
Pulmonary valve diastolic opening and dilated hypercontractile right ventricular outflow tract	M-movement of interventricular septum and/or posterior wall
Tall E wave on tricuspid Doppler flow	Tall E wave and small A wave ( $E/A \Rightarrow 2$ )
Dilated right atrium	Dilated left atrium
Large pericardial effusion	Pulmonary hypertension
Spontaneous contrast or intracavitary thrombi	Spontaneous contrast or intracavitary thrombi
Apical notch or shrunken right ventricle	Reduced longitudinal dimension of the left ventricle

In right EMF pressures in the right atrium, right ventricle, and pulmonary artery are equal both in form and amplitude, and angiograms show flattened apex, loss of trabeculated pattern, dilated and hypercontractile infundibulum, free tricuspid reflux, large right atrium and dilated cava veins.<sup>(68)</sup> Left EMF is characterised by very high left ventricular end-diastolic pressure with dip-plateau pattern, pulmonary hypertension variably damped by the presence of the RV disease, and the angiogram shows left apical obliteration with varying degree of mitral regurgitation.

Endomyocardial biopsy is not essential for the diagnosis of EMF in endemic areas. It can be misleading when tissue is obtained from unaffected sites and is technically difficult in areas of dense endocardial fibrous thickening.

#### Differential diagnosis

In Africa it is important to differentiate left EMF from mitral valve disease due to rheumatic heart disease. The large atria associated with small ventricles characteristic of bilateral EMF allow easy

differentiation from dilated cardiomyopathy. Finally, tuberculous and constrictive pericarditis must also be considered, as well as neoplastic infiltration by lymphomas, particularly in children and young adults.

#### Management

Although no specific therapy for EMF is available, amelioration of acute disease, heart failure and arrhythmias, can be achieved with corticosteroids, diuretics, vasodilators, digitalis, B-blockers and anticoagulants. The overall results of medical therapy have been improving lately but patients with advanced disease need large doses of drugs and frequent admissions to hospital for invasive procedures to alleviate effusions (pericardial, pleural and peritoneal) and control arrhythmias.

Surgery is indicated in patients in NYHA class III and IV since it increases survival and quality of life when compared to medical therapy.<sup>(69)</sup> It should be performed before irreversible cardiac and hepatic damage occurs.<sup>(70)</sup>

In Africa due to the lack of human and material resources for open-heart surgery in most endemic areas, the surgical experience has been growing slowly. A translational research project including surgical treatment is underway in Mozambique.<sup>(3)</sup> The results of surgery have been improving with the use of new surgical procedures based on better understanding of the pathophysiology of EMF and tailored to the structural abnormalities detected.<sup>(71)</sup>

### PERIPARTUM CARDIOMYOPATHY

#### Definition

Peripartum cardiomyopathy (PPCM) is a devastating form of heart failure in which left ventricular systolic dysfunction and symptoms of heart failure occur in a previously healthy women during the late stages of pregnancy or within a few months postpartum, usually in the last month of pregnancy and the first 5 months postpartum.<sup>(19,72)</sup>

#### Epidemiology

There are no large population studies on the incidence and prognosis of PPCM in Africa. Hospital-based studies report an incidence of 1:1 000 deliveries in South Africa<sup>(15)</sup> and 1:500

deliveries in Nigeria,<sup>(73)</sup> showing that the incidence is higher than that reported in other parts of the world.<sup>(15,19,20,74,75)</sup>

Although the highest incidence of PPCM has been reported in women > 30 years of age,<sup>(76)</sup> it can occur at any age and is frequently seen in young women in Africa and after their first pregnancy.

### Etiology and pathogenesis

The etiology of PPCM remains unknown but viral, autoimmune and idiopathic myocarditis are highly suggested.<sup>(19)</sup> Several hypotheses have been put forward namely myocarditis, viral infection, autoimmune factors, inflammatory cytokines, abnormal hemodynamic response to physiological changes in pregnancy, prolonged tocolysis and selenium deficiency.<sup>(76,77,78,79,80)</sup>

There are discrepancies in the incidence of myocarditis in PPCM that may be due to differences in timing of the myocardial biopsy.<sup>(81)</sup> While an incidence of myocarditis of about 78% has been reported in newly diagnosed PPCM patients,<sup>(81)</sup> failure to demonstrate the presence of myocarditis is also common.<sup>(82)</sup> There is also some evidence that inflammation – possibly related to autoimmunity – may play a role in the pathogenesis in early stages of the disease process.<sup>(83)</sup> More recently a study at a single tertiary level hospital in South Africa showed raised levels of inflammation markers as evidence for a role of apoptosis in PPCM patients.<sup>(84)</sup>

The major risk factors reported for PPCM are black race, advanced maternal age, multiple gestations, twin pregnancy, gestational hypertension and long-term tocolysis.<sup>(18,19,80)</sup>

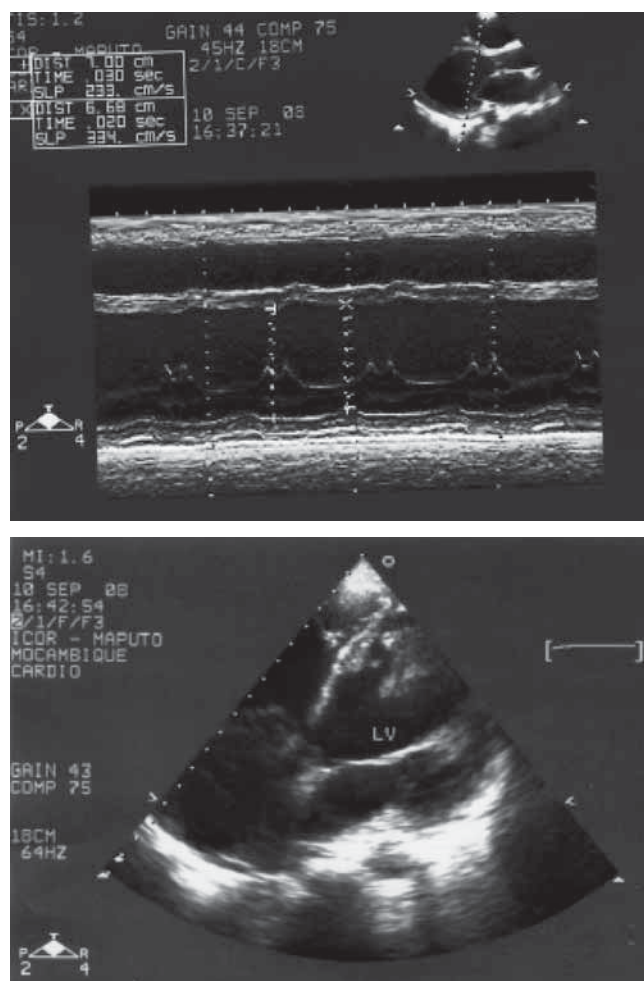
Although the pathophysiology remains largely unknown, a specific mechanism has emerged with the recent discovery of an oxidative stress-cathepsin D-I6-KDA prolactin cascade in experimental and human PPCM.<sup>(85)</sup>

### Clinical presentation and investigations

The clinical presentation of patients with PPCM is similar to that of patients with dilated cardiomyopathy. Patients with PPCM most commonly present with dyspnea but other frequent complaints include cough, orthopnoea, paroxysmal nocturnal dyspnea, haemoptysis, and chest discomfort. ECG findings may include sinus tachycardia, non-specific ST and T wave abnormali-

ties, and voltage abnormalities. The chest radiograph typically shows enlargement of the cardiac silhouette with evidence of pulmonary venous congestion or interstitial oedema, or both. On chest radiography there may be evidence of cardiomegaly, left ventricular hypertrophy, pulmonary oedema, pulmonary venous congestion and bilateral pleural effusion.

Doppler echocardiography is the most widely used procedure for diagnosis showing usually dilated ventricles with marked systolic dysfunction, commonly associated with atrial enlargement, mitral and tricuspid regurgitation, and a small pericardial effusion.<sup>(86)</sup> Elevated pulmonary artery pressure and pulmonary arterial hypertension are also seen in the majority of cases.<sup>(86)</sup> Ventricular thrombosis is common (Figure 3) and has been reported in up



**FIGURE 3:** Dilation of the ventricles, severe myocardial dysfunction and ventricular thrombi are characteristic features of peripartum cardiomyopathy.



to 53% of patients with peripartum cardiomyopathy.<sup>(76,87)</sup> Recent thrombi are more shaggy and irregular in configuration, whereas organised thrombi are more circumscribed and immobile.<sup>(88)</sup>

Some evidence exists for the usefulness of MRI for diagnosis, pathogenic and prognostic consideration in patients with PPCM.<sup>(89)</sup> Cardiac catheterisation can be used for evaluation of left ventricular function, obtaining endomyocardial biopsies and performing coronary angiography, but is not essential to diagnosis in most cases.

## Diagnosis

The criteria currently used for diagnosis of PPCM are symptoms of heart failure or echocardiographic diagnosis of left ventricular dysfunction (left ventricular ejection fraction  $<0.45$ ; left ventricular fractional shortening  $<30\%$ ; left ventricular end-diastolic dimension  $>2.7\text{cm/m}^2$  body surface area), occurring one month before or in the 5 months after delivery, in the absence of an alternative cause of heart failure and any recognisable heart disease before last month of pregnancy.<sup>(78,79)</sup>

## Differential diagnosis

Peripartum cardiomyopathy presenting as congestive heart failure affecting African women in late pregnancy or in the early puerperium, must be differentiated from dilated cardiomyopathy, endomyocardial fibrosis and HIV-related cardiomyopathy, which are also very common. Similarly, other secondary forms of cardiomyopathy must be ruled out, namely pre-eclampsia, infections, anemia, thiamine deficiency and alcoholism.

In women with post-natal pre-cordial pain, in which situation the differentiation can present a diagnostic dilemma,<sup>(90)</sup> symptoms of exercise-related chest pain, exertional dyspnea, and orthopnea point to a primary cardiac pathology, and the clinical signs of pulmonary oedema and gallop rhythm usually exclude a thromboembolic cause.

## Complications

The main complications of PPCM are thromboembolism, arrhythmias, organ failure, and obstetric and perinatal complications.

Systemic and pulmonary thromboembolism, described in a considerable number of patients with left ventricular dysfunction, is thought to be due to hypercoagulability and risk of thrombosis during pregnancy and postpartum period, including activation of coagulation factors, increase in plasma fibrinogen, and platelet adhesion. The risk of thrombosis is aggravated by the need for prolonged rest due to congestive heart failure.

Arrhythmias found in women with PPCM include sinus tachycardia, atrial and ventricular tachycardia, atrial and ventricular premature beats. Ventricular arrhythmia is thought to be the cause of sudden death reported in PPCM.

Organ failure is caused by passive congestion associated with hypoperfusion due to cardiac failure and low cardiac output.

Perinatal complications include premature delivery, small for date and low birth weight babies, intrauterine growth retardation and fetal deaths<sup>(91,92)</sup> and higher infant mortality.<sup>(77)</sup>

## Management

A multidisciplinary approach involving an obstetrician, cardiologist, anesthesiologist and perinatologist may be required to provide optimal care to PPCM patients.<sup>(78,84,87)</sup> The current management of this condition consists of medical therapy using inotropic support, diuretics, beta-blockers, vasodilators (angiotensin-converting enzyme inhibitors, nitrates or hydralazine) and anticoagulants. Although there is currently no consensus as to whether patients with depressed left ventricular function and sinus rhythm should be anticoagulated to prevent thrombus formation, PPCM presents a higher risk and might need aggressive and pre-emptive coagulation once the diagnosis is made.<sup>(93)</sup> The role of immunosuppression has not been clearly defined, but seems to have a place in myocarditis-positive PPCM patients.<sup>(94)</sup> Immunomodulation using pentoxifylline has been used due to its capacity to reduce production of TNF $\alpha$ , CRP and Fas/Apo-I (a marker of apoptosis), but further studies are needed to clarify its effects.<sup>(95,96)</sup> More recently, the use of bromocryptine (inhibitor of prolactine) was successful in preventing left ventricular dysfunction in subsequent pregnancies of women known to have had PPCM.<sup>(97)</sup>

Effective medical treatment reduces mortality rates and increases the number of women who fully recover left ventricular systolic function.<sup>(20,84)</sup> However, the adverse effects of medical therapy on

the fetus or breast-feeding infant must be borne in mind. While hyponatremia has been reported in infants born from mothers taking diuretics prepartum, angiotensin-converting enzyme inhibitors are absolutely contraindicated prepartum, when they may be associated with adverse fetal renal effects and an increase in neonatal mortality.<sup>(90)</sup> Beta-blockers are generally safe in pregnancy.<sup>(95)</sup>

Surgical management with cardiac transplantation is indicated in severe cases with progression of left ventricular dysfunction despite medical therapy. Mechanical ventricular assistance can be used as a bridge to transplantation.<sup>(98)</sup>

### Outcome

The course and outcome of this cardiomyopathy are largely unpredictable. Maternal mortality, initially reported to reach 85%,<sup>(76)</sup> has now decreased to 9%-50%.<sup>(17,84,91,99,100)</sup> About half patients with PPCM recover,<sup>(19,84,99)</sup> while 25% evolve to death within 3 months due to heart failure, arrhythmias or thromboembolism, and the remaining patients develop dilated cardiomyopathy (Figure 3). The overall prognosis has been improved with increase in the percentage of women who recover left ventricular function and reduction of mortality, due to advances in the therapeutics of heart failure in recent years, mainly the arrival of new drugs to treat heart failure, the benefits of cardiac transplantation and the use of mechanical ventricular assist systems.<sup>(98)</sup>

Recent studies show that Troponin T levels can predict persistent left ventricular dysfunction in peripartum cardiomyopathy<sup>(101)</sup> and found that baseline Fas/Apo-I and higher NHYA at presentation were the only predictors of mortality.<sup>(96)</sup> MRI using late gadolinium enhancement may be useful for the evaluation of the extent of myocardial damage and to predict the outcome of PPCM.<sup>(89)</sup>

### Risk of recurrence in future pregnancies

The risk of developing PPCM in subsequent pregnancies remains high,<sup>(19)</sup> although the factors involved in the prognosis are still not fully understood and diversity in clinical features of PPCM causes difficulties in making recommendations for future pregnancies.

The mechanism of recurrent symptomatic heart failure in patients with a history of PPCM and recovered left ventricular function has

been attributed to a significant physiological increase in blood volume, stroke volume and heart rate during pregnancy,<sup>(102)</sup> but the finding of marked depression of in left ventricular function with subsequent pregnancy suggests that worsening of symptoms are also due to reactivation of the underlying idiopathic process responsible for the development of cardiomyopathy in previous pregnancy.<sup>(103)</sup> While the outcome of subsequent pregnancies is better in women who have fully recovered heart function,<sup>(84)</sup> persistence of left ventricular dysfunction after 6 months indicates irreversible cardiomyopathy and portends worse prognosis.<sup>(18)</sup> Currently available data suggest that in patients with persistent left ventricular dysfunction strong recommendation to avoid additional pregnancies is warranted, while preconception counseling in patients with recovered left ventricular function is less consensual.<sup>(19,92,104)</sup>

### Research on neglected cardiomyopathies in Africa

Due to their obscure etiology and pathogenesis, the challenges posed to their diagnosis and management, and their poor overall prognosis, cardiomyopathies have always attracted the interest of the scientific community. However, while in developed countries research and availability of effective management options have lead to improvement in prognosis of those that are most prevalent, cardiomyopathies peculiar to Africa have been ignored for long time. This is demonstrated by the lack of studies on their incidence, prevalence, determinants and outcome of these diseases in Africa.<sup>(2)</sup>

Neglected cardiomyopathies are currently a cause of major concern to African individuals, health managers, cardiologists and researchers. However, due to lack of human and material resources for research in most endemic areas, there is need for the creation of networks of local researchers that will be dedicated to investigate these diseases. This effort could be supported and coordinated by continental health professional organisations, with the involvement of African universities and non-governmental organisations dedicated to delivery of health care, professional training and cardiovascular research. Academic and sponsoring institutions in the developed world should be supportive of projects designed and lead by local investigators.<sup>(105)</sup>

Particularly for EMF and PPCM most publications from Africa are several years old, based on small numbers of patients and/or using older criteria for diagnosis, which did not include echo-



cardiography. We are of the opinion that the proposed risk factors associated with these cardiomyopathies requires serious reevaluation and that actual incidence could be estimated using modified diagnostic criteria, particularly in endemic areas.

Herewith a description of two projects studying these entities in African countries: Mozambique and South Africa.

## Endomyocardial fibrosis project (Mozambique)

The Heart Institute of Mozambique is a non-governmental organisation lead by local cardiologists, devoted to diagnosis, treatment and prevention of cardiovascular diseases, as well as research into African-specific forms of cardiovascular diseases. It is a non-profitable institution that is established in Maputo city (the capital of Mozambique). Renowned cardiovascular teams from France, England, Portugal, Switzerland and Italy contribute with open-heart surgery performed in Mozambique periodically, while the local team is being trained. The research programme has been supported by the Magdi Yacoub Institute (London, UK), which has been sponsoring the training programme and the establishment of the research laboratories.

Large-scale studies using echocardiographic screening to determine the prevalence, incidence and determinants of EMF are being performed in a remote rural area with high prevalence of the disease in the south of Mozambique (Inharrime), situated 400kms from Maputo city, since January 2005. These community-based studies have been coupled with clinical and fundamental research, with the aim to understand the pathogenesis and mechanisms of the disease, and develop new approaches to the management of this condition.

Transthoracic echocardiography was used for the screening of 1 359 individuals randomly selected in the endemic rural area: 1 063 individuals at their houses and 296 children from local schools (Figure 4). Additionally, a National Clinical Registry has been established, including 196 patients referred from all parts of the country, which are being followed up. A total of 432 individuals with the diagnosis of endomyocardial fibrosis are therefore being studied, of which 236 were detected during community studies.

In reaching out to the population in its environment the initial stages of the disease that were not previously described, can now

be detected.<sup>(33)</sup> This ongoing research, through follow up of cohorts of individuals who are well characterised by echocardiography, gives a unique opportunity to define the natural history of EMF, investigate its determinants and define the mechanisms involved in the pathogenesis. On the other hand new therapeutic approaches have been evolved and applied with improvement of management and prognosis.<sup>(71)</sup>

## The Heart of Soweto Project (South Africa)

The Soweto Cardiovascular Research Unit was set up in January 2006 to co-ordinate a range of research into cardiovascular disease in Soweto, South Africa. It is a collaborative project, bringing together internationally renowned academics that will examine several questions in relation to the emergence of heart disease in Soweto and other African communities in epidemiological transition. The Heart of Soweto Study aims to address our poor understanding of the characteristics and burden imposed by cardiovascular disease in an African setting. It comprises projects with particular interest in peripartum and dilated cardiomyopathies, which are being undertaken through collaborative projects between Universities in South Africa, USA and Germany.<sup>(106)</sup>

An initial work identified 4 162 cases of cardiovascular disease, of which 1 593 newly diagnosed in 2006.<sup>(107)</sup> Among the 1 593 newly diagnosed cases, heart failure was the most common primary diagnosis (44% of cases) with most cases due to dilated cardio-



**FIGURE 4:** Echocardiographic screening in a remote rural area of Mozambique during community studies is being used for establishment of cohorts that will contribute to better understanding of the natural history and pathogenesis of endomyocardial fibrosis.

myopathy (36%) and largely confined to black African patients (91%).<sup>(107)</sup> The high incidence of PPCM in this community of South Africa has provided a unique opportunity to initiate studies of the mechanisms, clinical features and prognostic markers in this disease. A randomised clinical trial to explore bromocriptine as a new therapy is currently underway.

## CONCLUSIONS

These two projects show that there is awareness about the relevance of cardiomyopathies in Africa and that local cardiovascular specialists are willing to be the stakeholders for the movement aiming to revert the unacceptable situation of neglected cardiomyopathies in this continent. The emphasis of the research projects has been towards etiology and pathogenesis, with an ultimate goal of preventing the occurrence of cardiomyopathies and/or changing their natural history.

Future research should include prospective case-control studies to help identify the mechanisms of the disease, and define the role of environmental factors (such as parasites, viruses, nutritional factors, allergens) as well as that of immunogenetic susceptibility. New knowledge gained in several fields such as endothelial cell biology, inflammation, hemostasis, regulation of collagen synthesis, remodeling and mechanisms of fibrosis, must be incorporated into these research projects, aiming at altering the natural history and the management of these conditions.

These projects might allow the development of community-based programmes of health care in response to local cardiovascular problems. Importantly, in the process, the team of internationally renowned investigators will build local research capacity to develop sustainable programmes of research and high quality health services in African countries. Both the international collaboration in the medical field and the research outcomes will impact the lives of millions of individuals living in similar communities in Africa and other parts of the world.

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